Homologous Structures Among 2-Aminofluorene and Benzo[a]pyrene Diol Epoxide-DNA Adducts. Monique Cosman[1,*] Bing Mao[1], Brian E. Hingerty[2], Nicholas E. Geacintov[3], Suse Broyde[4] and Dinshaw J. Patel[1].

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Polycyclic aromatic amines (AA) and hydrocarbons (PAH) are environmental carcinogens present in products generated from fossil fuel combustion, tobacco smoke and certain methods of cooking. Two widely studied representative members of these classes of compounds are 2-aminofluorene (AF) and benzo[*a*]pyrene (BP). Both AF and BP can be metabolically activated to reactive intermediates which can bind covalently to DNA. The activated form of AF binds predominantly to the C8 position of guanine (AF-C8-dG), while the (+)- and (-)-*anti*-7,8-diol-9,10-epoxide derivatives of BP [(+)- and (-)-BPDE] bind primarily to the N^2 position of guanine (BP-N^2-dG). We have used a combined NMR-molecular mechanics approach to determine the solution structures of several AF and BPDE modified oligomer duplexes containing a site specific, and in the case of BPDE-DNA adducts, stereochemically-defined lesion. Important goals in this area of research are the characterization of structure-biological activity relationships and the definition of key structural features of ligand-DNA adducts which distinguish biologically active lesions from inactive ones. To date, we have identified several families of DNA adduct structures consisting of members having common conformational features. Here, we present an example of one such family of structures containing three DNA adducts:

(1) AF-C8-dG opposite a deletion site [Bing et al. (1995)*Biochemistry 34,* 6226-6238],

(2) (+)-t*rans-anti*-BP-N^2-dG opposite a deletion site [Cosman et al. (1994)*Biochemistry 33,* 11507-11517] and

(3) (-)-*cis-anti*-BP-N^2-dG opposite a cytosine [Cosman et al. (1995) *in preparation*],

in the DNA sequence context: d(CCATC*****GCTACC)·d(GGTAGNGATGG), where *****G denotes the modified guanine and N = deletion or cytosine. In each case, the aromatic ring system of AF or BP intercalates into the helix by displacing the modified guanine into the major groove. The displaced guanine base is inclined relative to the helix axis and stacks over the 5'-flanking cytosine. The Watson-Crick hydrogen bonding alignments of the remaining 10 base pairs, including the dG·dC base pairs located on either side of the modified guanine, remain intact. This structural homology among these AF and BP derived DNA adducts is independent of the ligand-DNA linkage site and suggests that hydrophobic stacking interactions between the aromatic ring system of the ligand and the neighboring DNA bases are important determinants in the formation of a base-displaced intercalation type conformation. Perhaps the common structural features of these AF and BP-DNA adducts are relevant in the expression of their mutagenic activities as well.
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